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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/506,079	02/16/2000	Joni Kristin Doherty	49321-1A	5713

7590 07/16/2004

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/506,079	DOHERTY ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,8-10,18-20 and 38-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8-10,18-20,and 38-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/21/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 21, 2004 has been entered.

Claims 1-3, 8-10, 18-20 and 38-49 are pending and examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections and Rejections Withdrawn:

3. The rejection of claim 18 under 35 U.S.C. 102(e) as being anticipated by Hudziak (U.S. Patent 6,399,063; issued June 4, 2002; effective filing date Jan. 25, 1988) is withdrawn in view of the amendment.

Claim Rejections Maintained and New Grounds of Rejection:

SEQUENCE RULES:

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Specifically, the nucleotide and amino acid sequences in Figures 1 and 8 are not identified with sequence identifiers, either in the Figure itself, or in the "Brief Description of the Drawings". Applicant is required to amend the specification and to amend both the CRF and paper copy of the sequence listing if the sequences in the Figures are new sequences.

Also, applicants should inspect SEQ ID NO: 2 for errors. It appears that SEQ ID NO: 2 contains an Asp in position 389 (in both the CRF and the paper copy), which is not included in SEQ ID NO: 15, which is a sequence that is supposed to be within the genus of SEQ ID NO: 2 (applicants' assertion in the amendment filed 4/21/2004). Also, the Asp in position 389 is not found in the prior art sequence.

APPLICANT IS GIVEN THE PERIOD OF THIS COMMUNICATION WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136. In no case may an applicant extend the period for response beyond the six-month statutory period. Applicant is requested to return a copy of the attached Notice to Comply with the response.

5. The rejection of claims 1-3, 8-10, 18-20 and 38-41 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for the reasons of record.

Applicants' arguments have been carefully considered, but are unpersuasive. The declaration of Gail M. Clinton, filed under 37 C.F.R. 1.132, has also been considered.

Applicants argue that the disclosure of Table 1 and Figure 1 and the discussion of Table 1 on page 33 of the specification provides support for the claimed genus of polypeptides. This is not persuasive because the disclosure of Table 1 is not commensurate in scope with the scope of the claimed genus. Table 1 discloses individual variants, including one that is to be specifically excluded, but does not disclose all the possible variants that could be predicted from generic

formula of SEQ ID NO: 1. Furthermore, the working examples of the specification that demonstrate the biological activity of Herstatin describe work that was done with the excluded sequence. Therefore, the argument that SEQ ID NO: 11 or SEQ ID NO: 12 may be excluded to form the currently claimed subgenus, because the specification contains a list of variants, is not sufficient because the currently claimed subgenus is broader than what is disclosed in Table 1 and because most of the specification appears to be directed to teachings concerning the biological function and activity of the excluded species.

6. Claims 1-3, 8-10, 18-20 and 38-49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed inventions are drawn to polypeptides and pharmaceutical compositions comprising polypeptides that are variants of Herstatin, a polypeptide known in the art (see Doherty, J.K. et al., Proc. Natl. Acad. Sci. USA; cited in the IDS ; and U.S. Patent 6,414,130; issued July 20, 2002; previously cited). The claimed inventions specifically exclude Herstatin. Claims 42-49 are drawn to a single species of variant.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the

relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

The claimed inventions are not enabled by the disclosure of the specification, because the disclosure of the specification confines its teachings to setting forth the amino acid sequence of a number of the variants included within the claimed genus, but fails to describe the biological activity of any variant that is within the scope of the claims. The specification provides data demonstrating that Herstatin, a specifically excluded species, binds to the Her-2 receptor and inhibits dimerization of the receptor and inhibits tyrosine phosphorylation activity of Her-2, and thus appears to inhibit the biological activity of Her-2. Therefore, Herstatin appears to be useful as a tumor cell inhibitor, because it has the ability to inhibit the growth-promoting activity of Her-2.

However, the specification contains no data for any variants that are included within the scope of the claims, and it is not clear that the claimed variants possess the same biological functions as that of Herstatin, and therefore, it is not clear if the claimed biological variants could be used in the same way as is contemplated for Herstatin. Additionally, the specification asserts that the variations in the amino acid sequence of Herstatin could lead to altered biochemical and biological properties among the protein variants (see page 16, lines 13-15). It is well known in the prior art that the relationship between the primary amino acid sequence and protein function is highly unpredictable. For example, Bowie et al (Science, 247: 1306-1310, 1990) teaches that while it is known that many amino acid substitutions are possible in any given protein, the position with the protein sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Burgess et al (J. Cell Biology, 111:

2129-2138, 1990) teaches that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Lazar et al (Molecular and Cellular Biology, 8: 1247-1252, 1988) teaches that replacement of aspartic acid at position 47 with alanine or asparagines does not affect biological activity while replacement with serine or glutamic acid sharply reduces the biological activity of the protein. These references demonstrate that even a single amino acid substitution can dramatically affect the biological activity and characteristics of a protein. Thus, while the claimed variants may possibly have similar biological functions to that of Herstatin, the biological function of the claimed variants is unpredictable. The determination of the biological function of each of the possible variants would require further experimentation. This further experimentation would be an undue burden because it would be experimentation to discover a use for the claimed inventions and would constitute experimentation on the invention itself.

Therefore, because the claimed variants comprise amino acid substitutions coupled with the lack of working examples directed to any of the variants that are within the scope of the claims, the specification lacks teachings of the biological function of the claimed variants. The skilled worker would have to conduct further and undue experimentation to establish the biological function of the claimed variants before the skilled worker would know how to use the claimed inventions.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

Anne L. Holleran
Patent Examiner
July 13, 2004

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER
7/14/2004

Notice to Comply With Sequence Rules	Application No.	Applicant(s)	
	09/506,079	DOHERTY ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

X 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 8230, May 1, 1990.

___ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

___ 3. A copy of the "Sequence Listing" in Computer Readable Form (CRF) has not been submitted as required by 37 C.F.R. 1.821(e).

___ 4. A copy of the "Sequence Listing" in Computer Readable Form (CRF) has been submitted. However, the content of the CRF does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

___ 5. The Computer Readable Form (CRF) that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute CRF must be submitted as required by 37 C.F.R. 1.825(d).

___ 6. The paper copy of the "Sequence Listing" is not the same as the Computer Readable Form (CRF) of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

X 7. Other: Sequences in Figures that do not have a sequence identifier

Applicant Must Provide:

X An initial or substitute copy of the **CRF** "Sequence Listing".

X An initial or substitute **paper copy** of the "Sequence Listing", as well as an amendment directing its entry into the specification.

X A statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
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